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Co-infections, secondary infections, and antimicrobial use in patients hospitalised with COVID-19 during the first pandemic wave from the ISARIC WHO CCP-UK study: a multicentre, prospective cohort study

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Summary

Background Microbiological characterisation of co-infections and secondary infections in patients with COVID-19 is lacking, and antimicrobial use is high. We aimed to describe microbiologically confirmed co-infections and secondary infections, and antimicrobial use, in patients admitted to hospital with COVID-19.

Methods The International Severe Acute Respiratory and Emerging Infections Consortium (ISARIC) WHO Clinical Characterisation Protocol UK (CCP-UK) study is an ongoing, prospective cohort study recruiting inpatients from 260 hospitals in England, Scotland, and Wales, conducted by the ISARIC Coronavirus Clinical Characterisation Consortium. Patients with a confirmed or clinician-defined high likelihood of SARS-CoV-2 infection were eligible for inclusion in the ISARIC WHO CCP-UK study. For this specific study, we excluded patients with a recorded negative SARS-CoV-2 test result and those without a recorded outcome at 28 days after admission. Demographic, clinical, laboratory, therapeutic, and outcome data were collected using a prespecified case report form. Organisms considered clinically insignificant were excluded.

Findings We analysed data from 48 902 patients admitted to hospital between Feb 6 and June 8, 2020. The median patient age was 74 years (IQR 59–84) and 20 786 (42·6%) of 48 765 patients were female. Microbiological investigations were recorded for 8649 (17·7%) of 48 902 patients, with clinically significant COVID-19-related respiratory or bloodstream culture results recorded for 1107 patients. 762 (70·6%) of 1080 infections were secondary, occurring more than 2 days after hospital admission. *Staphylococcus aureus* and *Haemophilus influenzae* were the most common pathogens causing respiratory co-infections (diagnosed ≤ 2 days after admission), with Enterobacteriaceae and *S aureus* most common in secondary respiratory infections. Bloodstream infections were most frequently caused by *Escherichia coli* and *S aureus*. Among patients with available data, 13 390 (37·0%) of 36 145 had received antimicrobials in the community for this illness episode before hospital admission and 39 258 (85·2%) of 46 061 patients with inpatient antimicrobial data received one or more antimicrobials at some point during their admission (highest for patients in critical care). We identified frequent use of broad-spectrum agents and use of carbapenems rather than carbapenem-sparing alternatives.

Interpretation In patients admitted to hospital with COVID-19, microbiologically confirmed bacterial infections are rare, and more likely to be secondary infections. Gram-negative organisms and *S aureus* are the predominant pathogens. The frequency and nature of antimicrobial use are concerning, but tractable targets for stewardship interventions exist.

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Introduction

Bacterial co-infections and secondary infections are commonly identified in severe influenza (23% in a meta-analysis)¹ and other severe respiratory viral

infections, in which they are associated with increased morbidity and mortality.² National and international COVID-19 guidelines vary in their recommendations on empirical antimicrobial therapy—some recommend

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Research in context

Evidence before this study

An understanding of co-infections, secondary infections, and patterns of antimicrobial use in patients with COVID-19 is required to inform optimal empirical antimicrobial management strategies. We searched PubMed on Dec 29, 2020, for studies published in English, using the keywords "COVID-19", "SARS-CoV-2", "bacterial infection", "bacterial pneumonia", "superinfection", "co-infection", "secondary infection", and "nosocomial infection". Systematic reviews were included in the search. A low incidence of bacterial respiratory and bloodstream infections has been consistently reported in patients admitted to hospital with COVID-19. This finding is supported by a systematic review and meta-analysis, but individual studies lack granularity in microbiological and clinical details, are retrospective, and report on small cohorts. The timing of infection (co-infection or secondary infection) is often unknown. Reporting of positive results has lacked species-level detail on cultured organisms and exclusion of clinically irrelevant pathogens. PCR-based bacterial diagnosis is associated with higher pathogen detection than culture-based methods. Antimicrobial use in inpatients appears to be high, but studies infrequently report the drug classes used.

Added value of this study

This is a large, multicentre, prospective cohort study reporting microbiological findings and antimicrobial use in patients admitted to hospital with COVID-19 undergoing standardised microbiological investigation of samples submitted by clinical teams (UK Standards for Microbiology Investigations).

Microbiologically confirmed bacterial co-infection (≤ 2 days after admission) and secondary infections (> 2 days after admission) were uncommon in patients admitted to hospital with COVID-19, supporting the findings of a meta-analysis of smaller studies. When they did occur, bloodstream and respiratory infections were more likely to be secondary infections and Gram-negative organisms and *Staphylococcus aureus* were key aetiological agents, adding granularity in microbiological detail. Aetiology was affected by the timing of infection onset (co-infection or secondary infection), critical care admission, and chronic pulmonary disease. We confirmed high inpatient antimicrobial usage, additionally finding evidence of regional variation, frequent use of broad-spectrum empirical therapy for lower respiratory tract infections (β -lactam- β -lactamase inhibitor combinations), and use of carbapenems rather than carbapenem-sparing alternatives.

Implications of all the available evidence

Bacterial co-infections and secondary infections are rare in patients admitted to hospital with COVID-19. Most infections are secondary. Gram-negative organisms and *S aureus* are important pathogens and should be considered when designing empirical antimicrobial guidelines, but emphasis should be placed on restricting empirical prescribing, especially at hospital admission. The high frequency and nature of inpatient antimicrobial use might have long-term negative consequences for antimicrobial resistance. Specific targets exist for antimicrobial stewardship and should be integrated into COVID-19 patient care pathways.

empirical antimicrobial therapy in severe disease,^{3,4} whereas others do not.⁵ UK guidelines advise against empirical therapy when lower respiratory tract infection is thought to be due to COVID-19, without specific evidence of bacterial infection.^{6,7} Living systematic reviews and meta-analyses have reported a low prevalence of confirmed bacterial co-infection (8%), but a high proportion of patients with COVID-19 received antimicrobials (pooled prevalence 75%).^{8,9} The collective implication of these studies is a widespread failure of antimicrobial stewardship with the potential to worsen the global antimicrobial resistance crisis.¹⁰

Most studies to date have been retrospective with small sample sizes, and few have systematically reported the spectrum of bacteria, timing of infection onset, or described the frequency and nature of antimicrobials used to treat them. There is an urgent need to characterise the causes of bacterial infections in patients admitted to hospital with COVID-19 to determine optimal empirical antimicrobial management strategies and identify targets for antimicrobial stewardship interventions.

In this prospective, multicentre, cohort study of patients admitted to hospital with COVID-19, we aimed to report

the microbiological details of laboratory-confirmed co-infections and secondary infections identified by culture-based diagnostics, assess the effect of COVID-19-related co-infection on in-hospital mortality among patients admitted to critical care, and evaluate the nature of antimicrobial usage.

Methods

Study design and setting

The International Severe Acute Respiratory and Emerging Infections Consortium (ISARIC) WHO Clinical Characterisation Protocol UK (CCP-UK) study is an ongoing, prospective cohort study recruiting inpatients from 260 hospitals in England, Scotland, and Wales (National Institute for Health Research [NIHR] Clinical Research Network Central Portfolio Management System ID 14152) and conducted by the ISARIC Coronavirus Clinical Characterisation Consortium (ISARIC4C). Ethics approval was given by the South Central—Oxford C Research Ethics Committee in England (13/SC/0149), the Scotland A Research Ethics Committee (20/SS/0028), and the WHO Ethics Review Committee (RPC571 and RPC572; April, 2013). The study protocol and further details are available online.¹¹ This report of microbiological findings

and antimicrobial use from the study has been prepared in accordance with the STROBE statement.

Study participants and data collection

Patients with a confirmed or clinician-defined high likelihood of SARS-CoV-2 infection were eligible for inclusion in the ISARIC WHO CCP-UK study. For this specific study, we excluded patients with a recorded negative SARS-CoV-2 test result and those without a recorded outcome at 28 days after admission (discharged alive and expected to survive, palliative discharge [not expected to survive], ongoing hospitalisation, transfer to another facility [eg, for rehabilitation], or death). Demographic, clinical, laboratory, therapeutic, and outcome data were collected using a prespecified case report form. Comorbidities were defined by a modified Charlson comorbidity index and obesity was clinician defined. Data were uploaded to a Research Electronic Data Capture Database (REDCap; Vanderbilt University, Nashville, TN USA; hosted by University of Oxford, Oxford, UK).¹² The requirement for consent for data collection was waived in view of the public health emergency.

Infection data processing

Microbiological data comprising organism name(s), specimen type, result status, and date of sample were recorded as a combination of dropdown fields and free text in REDCap. Results of superficial microbiology, screening swabs, and serology were excluded because of insufficient clinical information to allow interpretation. Additionally, respiratory viruses other than SARS-CoV-2 were excluded since most laboratories prioritised SARS-CoV-2 over multiplex PCR testing during the first wave of the pandemic. Except for urine samples, staphylococci, other than *Staphylococcus aureus* and *Staphylococcus lugdunensis*, were considered clinically insignificant and excluded. Unspecified organisms (including positive microscopy findings with no culture result recorded) and results recorded as mixed growth or contaminant were excluded from all sample types. *Corynebacterium* sp and *Cutibacterium* sp were excluded from blood cultures. *Candida* sp were excluded from respiratory samples.

Positive cultures from blood, sputum, or deep respiratory tract (endotracheal aspirate, bronchoalveolar lavage, and pleural fluid) samples were considered possible COVID-19-related infections, while growth from other sample types was considered unrelated. Clinically significant positive results from samples collected within 2 days of admission were categorised as co-infections, and those collected more than 2 days after admission as secondary infections, synonymous with hospital onset or hospital-acquired infection.¹³ A patient could be recorded as having multiple infections, based on different sample types and different timepoints, during their admission.

Antimicrobials prescribed over the course of admission were entered as free text and mapped to drug names found in the UK National Health Service Technology Reference Data Update Distribution system.

Statistical analysis

Categorical variables are summarised as frequencies and percentages. Continuous variables are presented as means and SDs or medians and IQRs, depending on data distribution. Analysis of antimicrobial co-occurrence was done using the Jaccard similarity index and represented visually as heatmaps. $p \leq 0.05$ was considered to indicate a statistically significant difference. All statistical analyses were done using R version 3.6.3 using the *Tidverse*, *finalfit*, *stringdist*, and *fuzzyjoin* packages.

Role of the funding source

The funder of the study had no role in study design, data collection, data analysis, data interpretation, or writing of the report.

Results

We analysed data from 48 902 patients admitted to hospital between Feb 6 and June 8, 2020 (figure 1). The median patient age was 74 years (IQR 59–84) and 20786 (42.6%) of 48765 patients were female (table). The most common comorbidities were chronic cardiac disease and chronic pulmonary disease excluding asthma (table). 13 390 (37.0%) of 36145 patients had received antimicrobials in the community for this illness episode before hospital admission. Vital signs and laboratory results on admission are shown in the appendix (p 1). 31422 (69.2%) of 45420 patients received supplemental oxygen during their hospital stay, 6755 (14.9%) of 45420 patients received non-invasive ventilation, and 4241 (9.3%) of 45607 patients received invasive mechanical ventilation (table). 7090 (14.5%) of 48 902 patients required admission to critical care (high dependency or intensive care unit). 15 392 (31.5%) of 48 902 inpatients died in hospital.

Microbiological investigations were recorded for 8649 (17.7%) of 48 902 patients (figure 1; appendix p 1). Characteristics of this subgroup of patients are presented in the appendix (p 2). After exclusion of negative and non-significant results, we observed 2109 clinically significant results for 1942 patients. Patients admitted to critical care were more likely to have a documented blood or respiratory culture than ward-level patients (2163 [30.5%] of 7090 patients vs 5430 [13.0%] of 41812 patients; $p < 0.0001$). Positivity rates of recorded cultures were high—602 (42.1%) of 1429 cultures for sputum, 207 (51.5%) of 402 cultures for deep respiratory samples, and 500 (8.1%) of 6157 cultures for blood. We concluded that there was a bias towards recording positive results; therefore, we elected not to estimate the incidence of any infection within the cohort, restricting the reporting of proportions to identified organisms within positive samples.

See Online for appendix

	n	Patients with COVID-19
Demographics		
Sex	48 765	..
Male	..	27 979 (57.4%)
Female	..	20 786 (42.6%)
Age, years	48 902	74.0 (59.0–84.0)
Comorbidities		
Chronic cardiac disease	45 781	14 775 (32.3%)
Hypertension	22 006	10 645 (48.4%)
Chronic pulmonary disease	45 909	13 169 (28.7%)
Immunocompromise	25 742	7548 (29.3%)
Asthma	45 470	6309 (13.9%)
Chronic kidney disease	45 451	8092 (17.8%)
Chronic liver disease (moderate or severe)	45 001	867 (1.9%)
Chronic liver disease (mild)	44 880	683 (1.5%)
Chronic neurological disease	45 187	5747 (12.7%)
Current malignancy	45 067	4730 (10.5%)
Chronic haematological disease	45 019	1984 (4.4%)
HIV/AIDS	44 510	184 (0.4%)
Obesity*	41 058	4877 (11.9%)
Diabetes	46 180	13 581 (29.4%)
Rheumatological disease	44 946	5065 (11.3%)
Dementia	45 310	7534 (16.6%)
Smoking	31 125	..
Never	..	17 953 (57.7%)
Former	..	10 825 (34.8%)
Current	..	2347 (7.5%)
Pre-admission		
Symptom duration before admission, days	..	4.0 (1.0–8.0)
Receipt of antimicrobials before admission	36 145	13 390 (37.0%)
Maximum level of respiratory support		
Non-invasive ventilation	45 420	6755 (14.9%)
Invasive mechanical ventilation	45 607	4241 (9.3%)
Other organ support		
Renal replacement therapy	44 803	1508 (3.4%)
Vasopressors	44 672	2987 (6.7%)
Medical management		
Antibacterial	46 061	39 258 (85.2%)
Antifungal	48 902	309 (0.6%)
Corticosteroids	48 902	4850 (9.9%)
Outcomes		
Outcome at ≥28 days	48 902	..
Discharged alive and expected to survive	..	28 819 (58.9%)
Ongoing hospitalisation	..	1186 (2.4%)
Transfer to other facility	..	2623 (5.4%)
Inpatient death	..	15 392 (31.5%)
Palliative discharge	..	869 (1.8%)
Unknown or awaited	..	13 (<0.1%)
Length of stay, days†	..	9.0 (4.0–17.0)

Data are n (%) or median (IQR). *Clinician defined. †Excludes patients remaining in hospital after 28 days.

Table: Baseline characteristics, management, and outcomes of a cohort of 48 902 patients with COVID-19

We identified 1107 patients with COVID-19-related infections (positive blood, sputum, or deep respiratory cultures) and 1002 patients with unrelated infections (urine, abdominopelvic, or pus or abscess cultures). For microbiologically confirmed COVID-19-related infections where sample timing was known, 762 (70.6%) of 1080 infections were secondary, occurring more than 2 days after hospital admission. Among patients admitted to critical care, we found no association between patients identified to have a respiratory or bloodstream infection and inpatient mortality on univariable analysis (unadjusted odds ratio 1.02, 95% CI 0.86–1.22; $p=0.81$).

607 respiratory infections were recorded. Most culture-positive respiratory samples represented secondary infections (919 [84.9%] of 1082 sputum and deep respiratory cultures; figure 2A). In lower respiratory tract co-infections (within 2 days of admission), *S aureus* (21 [17.8%] of 118 organisms), *Haemophilus influenzae* (15 [12.7%] organisms), and *Pseudomonas aeruginosa* (11 [9.3%] organisms) were most frequently identified in sputum (figure 2). *Streptococcus pneumoniae* was

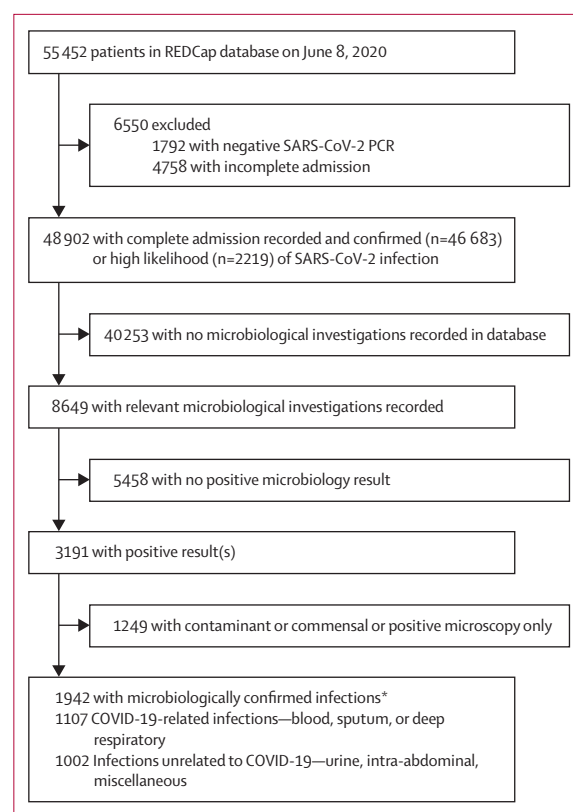
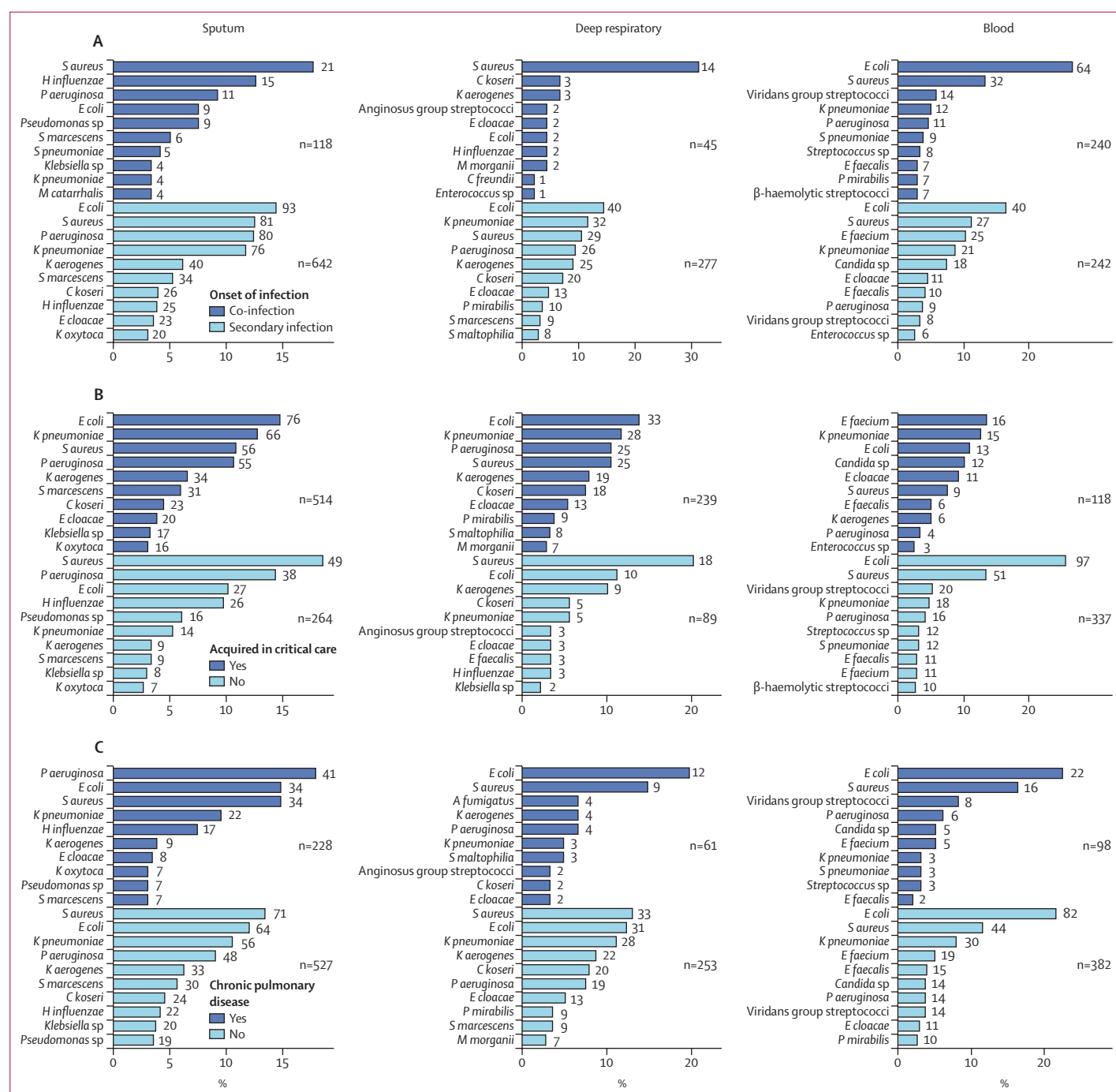


Figure 1: Study flowchart

A complete admission was considered an outcome recorded at 28 days or earlier, and could either be a final outcome (eg, death or discharged alive) or documentation the patient remained in hospital. Relevant microbiological investigations were blood cultures, sputum, deep respiratory (endotracheal aspirates, bronchoalveolar lavage, and pleural fluid), urine, abdominopelvic, or pus samples from abscesses. *Some patients had both a COVID-19 related and unrelated infection.

infrequently cultured (five [4.2%] of 118 organisms). Among deep respiratory samples identifying co-infection, *S aureus* was the predominant organism (14 [31.1%] of 45 organisms). *S aureus* was also a common cause of secondary lower respiratory tract infections (sputum 81 [12.6%] of 642 organisms; deep respiratory 29 [10.5%] of 277 organisms), but most organisms were Gram-negative, including *Escherichia coli* (sputum

93 [14.5%] of 642 organisms; deep respiratory 40 [14.4%] of 277 organisms), *P aeruginosa* (sputum 80 [12.5%] of 642 organisms; deep respiratory 26 [9.4%] of 277 organisms), *Klebsiella pneumoniae* (sputum 76 [11.8%] of 642 organisms; deep respiratory 32 [11.6%] of 277 organisms), *Klebsiella aerogenes* (sputum 40 [6.2%] of 642 organisms; deep respiratory 25 [9.0%] of 277 organisms), and *Citrobacter koseri* (sputum 26 [4.0%]



(Figure 2 continues on next page)

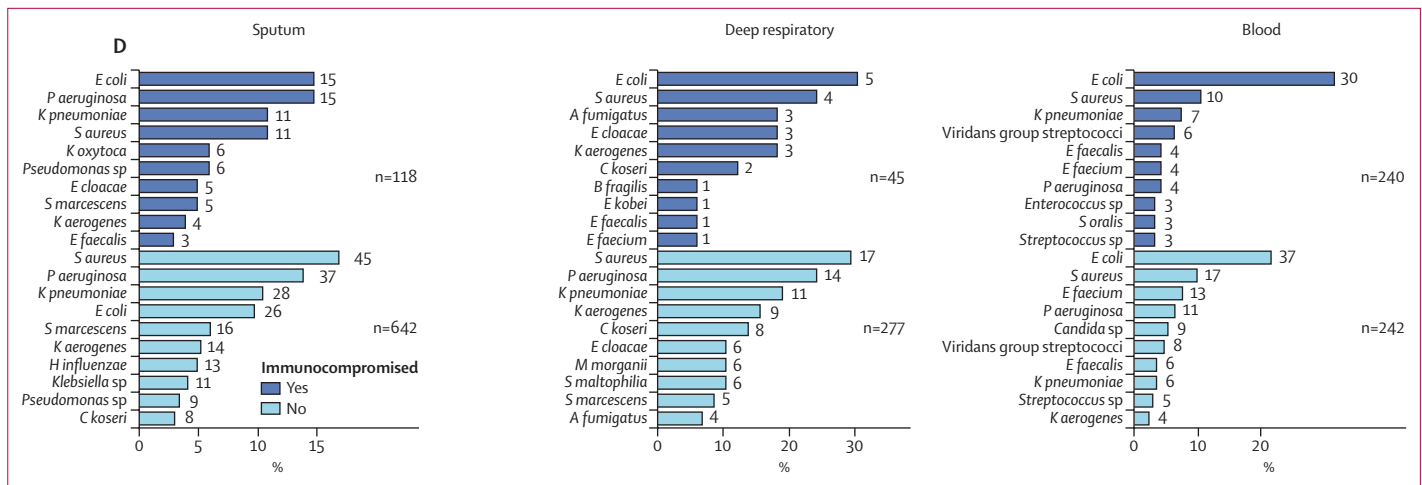


Figure 2: Cause of microbiologically confirmed respiratory and bloodstream infections

The ten most identified pathogens from sputum, deep respiratory, and blood cultures, as a percentage of all positive samples of that type. The number at the end of each bar represents the total number of positive samples for the pathogen. Numbers annotated on the plots indicate the total number of organisms for each subgroup. Deep respiratory samples are endotracheal aspirates, bronchoalveolar lavage, and pleural fluid. Pathogen identification is stratified into sample obtained <2 days (co-infection) or >2 days (secondary infection) from admission to hospital (A); sample obtained <1 day or >1 day after admission to critical care (B); presence or absence of chronic pulmonary disease (C); and presence or absence of immunocompromise (D). *S. aureus*=*Staphylococcus aureus*. *H. influenzae*=*Haemophilus influenzae*. *P. aeruginosa*=*Pseudomonas aeruginosa*. *E. coli*=*Escherichia coli*. *S. marcescens*=*Serratia marcescens*. *S. pneumoniae*=*Streptococcus pneumoniae*. *K. pneumoniae*=*Klebsiella pneumoniae*. *M. catarrhalis*=*Moraxella catarrhalis*. *K. aerogenes*=*Klebsiella aerogenes*. *C. koseri*=*Citrobacter koseri*. *E. cloacae*=*Enterobacter cloacae*. *K. oxytoca*=*Klebsiella oxytoca*. *M. morganii*=*Morganella morganii*. *C. freundii*=*Citrobacter freundii*. *P. mirabilis*=*Proteus mirabilis*. *S. maltophilia*=*Stenotrophomonas maltophilia*. *E. faecalis*=*Enterococcus faecalis*. *E. faecium*=*Enterococcus faecium*. *A. fumigatus*=*Aspergillus fumigatus*. *B. fragilis*=*Bacteroides fragilis*. *E. kobei*=*Enterobacter kobei*. *S. oralis*=*Streptococcus oralis*.

of 642 organisms; deep respiratory 20 [7.2%] of 277 organisms).

When stratified by critical care admission status, 174 (72.8%) of 239 organisms were identified from deep respiratory samples obtained more than 1 day after critical care admission (figure 2B). Deep respiratory samples included bronchoalveolar lavage, endotracheal aspirate, and other distal lung samples; the microbiological results from each of these sample types were similar (appendix pp 3, 5). In the critical care setting, *E. coli* was the most common cause of lower respiratory tract infections (sputum 76 [14.8%] of 514 organisms; deep respiratory 33 [13.8%] of 239 organisms), followed by *K. pneumoniae* (sputum 66 [12.8%] of 514 organisms; deep respiratory 28 [11.7%] of 239 organisms), *S. aureus* (sputum 56 [10.9%] of 514 organisms; deep respiratory 25 [10.5%] of 239 organisms), and *P. aeruginosa* (sputum 55 [10.7%] of 514 organisms; deep respiratory 25 [10.5%] of 239 organisms). Several opportunistic organisms—such as *C. koseri*, *Stenotrophomonas maltophilia*, and *Morganella morganii*—were cultured from respiratory samples obtained in critical care. Among non-critical care patients, *S. aureus* was the most common organism in sputum (49 [18.6%] of 264 organisms) and deep respiratory samples (18 [20.2%] of 89 organisms), followed by *P. aeruginosa* (sputum 38 [14.4%] of 264 organisms; deep respiratory none of 89 organisms), *E. coli* (sputum 27 [10.2%] of 264 organisms; deep respiratory ten [11.2%] of 89 organisms), and *H. influenzae* (sputum 26 [9.8%] of 264 organisms; deep respiratory three [3.4%] of 89 organisms).

Sputum microbiology differed between patients with and without chronic lung disease (figure 2C). Although *S. aureus* (71 [13.5%] of 527 organisms), *E. coli* (64 [12.1%] of 527 organisms), and *K. pneumoniae* (56 [10.6%] of 527 organisms) were the predominant organisms detected in patients without chronic respiratory disease, *P. aeruginosa* (41 [18.0%] of 228 organisms), *E. coli* (34 [14.9%] of 228 organisms), and *S. aureus* (34 [14.9%] of 228 organisms) were the most frequently isolated in those with chronic lung disease. *Aspergillus fumigatus* was also cultured from deep respiratory samples in four patients with chronic lung disease, three of whom were immunocompromised (clinician-defined or in receipt of immunomodulatory therapy before admission to hospital). We observed no other major differences in lower respiratory tract microbiology stratified by immune status (figure 2D).

With regard to blood cultures, 500 clinically significant results were recorded (appendix p 1). *E. coli* (104 [20.8%] of 500 organisms) was the most frequently identified pathogen, followed by *S. aureus* (59 [11.8%]; figure 2) and *K. pneumoniae* (33 [6.6%]; figure 2). Pneumococcal bacteraemia was uncommon (nine [1.8%] of 500 organisms). In bacteraemia occurring more than 1 day after admission to critical care, *Enterococcus faecium* (16 organisms) and *K. pneumoniae* (15 organisms) were the most common pathogens. Candidaemia (12 organisms) was also more common. We observed no major differences when patients were stratified by immune status but viridans group streptococci and *P. aeruginosa* were over-represented in patients with chronic lung disease. To determine the source of bacteraemia, we identified patients with the same organism

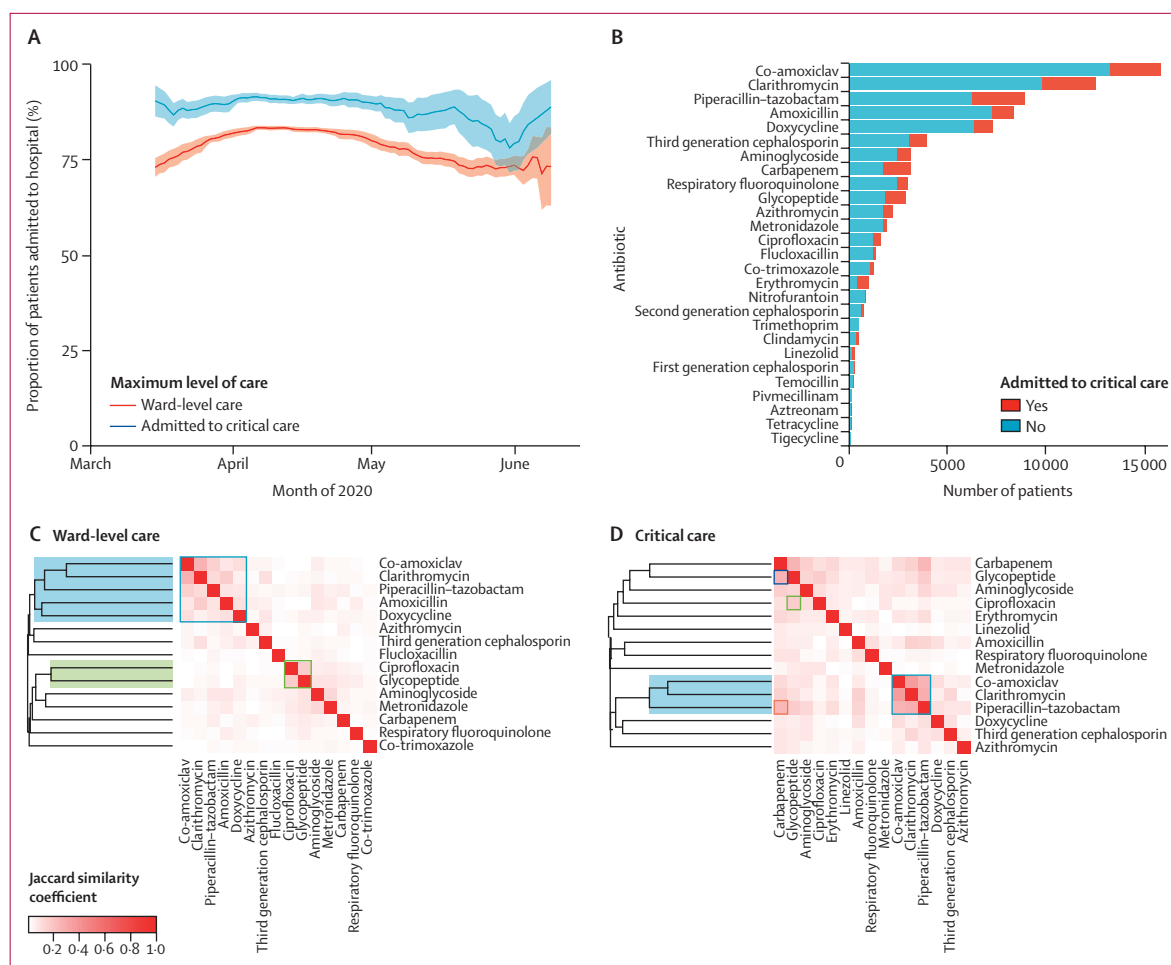


Figure 3: Frequency and nature of antimicrobial use

(A) The proportion of inpatients receiving antimicrobials between March and June, 2020, stratified by level of care. Data show rolling mean over a window of 14 days. Dotted lines represent 95% CIs. (B) Specific antimicrobials used, stratified by level of care or critical care. Co-use of specific antimicrobials in patients receiving ward-level care (C) and patients admitted to critical care (D), highlighting antimicrobials used for lower respiratory tract infection (blue box and shading), a signature of prescribing in response to penicillin allergy (green box and shading), carbapenem and glycopeptide usage in critical care (D only; blue box) and piperacillin-tazobactam and carbapenem in critical care (D only; orange box). The greater the intensity of red shading, the greater the correlation of antimicrobial use measured by Jaccard distance. Dendrograms show the result of hierarchical clustering. Data available for 46 061 patients.

isolated from another sample type. Generally, we found little overlap between blood and other cultures, with more overlap observed for sputum and deep respiratory samples compared with other samples (appendix p 4). *S aureus* was cultured from a sputum sample in nine (15.0%) of 60 patients with *S aureus* bacteraemia. Despite the frequency of *E coli* bacteraemia, *E coli* bacteriuria in the same patients was infrequently identified (appendix p 4).

39 258 (85.2%) of 46 061 patients with inpatient antimicrobial data received one or more antimicrobials at some point during their admission. Antimicrobial use was highest in March and April, 2020, both among patients admitted and not admitted to critical care (figure 3A). This proportion reduced over the course of May, 2020. We found substantial regional differences in prescribing, in both the proportion of patients given antimicrobials (figure 4; appendix pp 6–7) and the type of

antimicrobial prescribed (appendix pp 6–7). Across all regions, a higher proportion of patients admitted to critical care received antimicrobials compared with ward-level patients. The proportion of patients receiving antimicrobials fell or remained static across most regions; the largest decline was observed in Scotland in critical care (150 [87.2%] of 172 patients in March, 2020, to 12 [66.7%] of 18 patients in May, 2020), and in the southwest of England in ward-level care (678 [82.7%] of 820 patients in March, 2020, to 200 [63.9%] of 313 patients in May, 2020). Amoxicillin was more commonly prescribed in Scotland and Wales compared with England, whereas co-amoxiclav prescription was higher in England than Scotland and Wales, particularly among ward-level patients (appendix pp 6–7). Piperacillin-tazobactam prescription among ward-level patients was higher in Wales and certain English regions, including

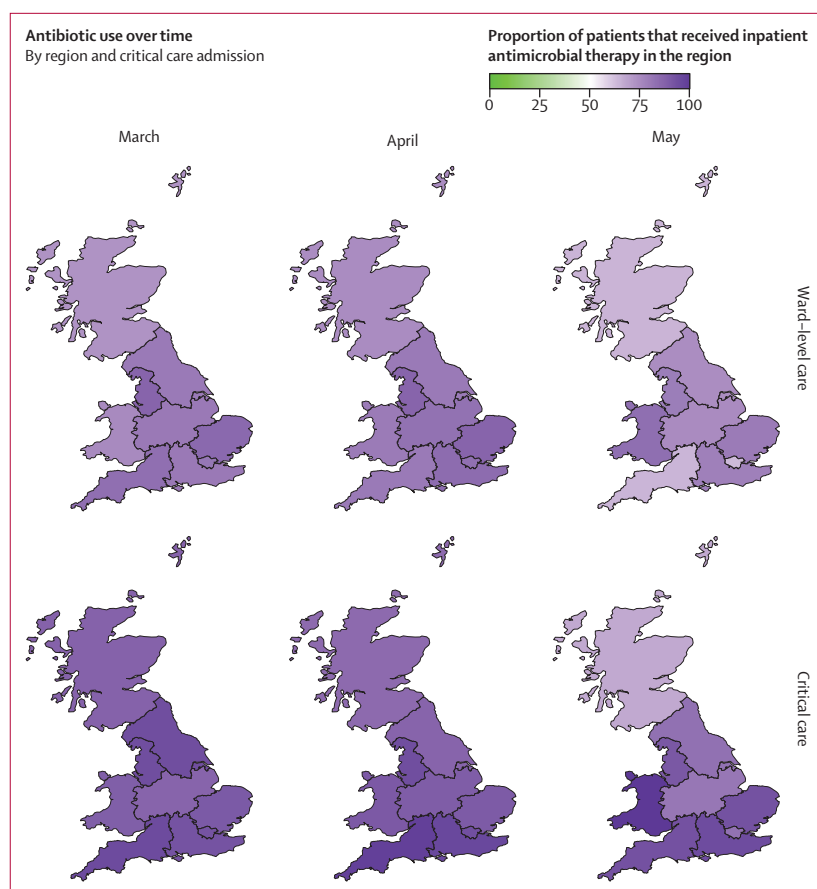


Figure 4: Geographical variation in antimicrobial use over time
Maps are divided into Scotland, Wales, and regions of England (northeast and Yorkshire, northwest, midlands, east, southeast, southwest, and London). Purple shading of regions represents the percentage of patients who received antimicrobial therapy during their hospital admission, stratified by month of admission (March, April, and May) and by level of care (ward-level or critical care). Data available for 46 061 patients.

the northwest, southwest, east, and northeast and Yorkshire, compared with other regions.

β -lactam- β -lactamase inhibitor combinations were among the top three most prescribed antimicrobials, accounting for 30.0% of total prescriptions (co-amoxiclav 19.2%, piperacillin-tazobactam 10.8%; figure 3B). Narrower-spectrum antimicrobials used for the treatment of lower respiratory tract infections accounted for fewer prescriptions (amoxicillin 10.2% and doxycycline 8.9%). Consistent with lower respiratory tract infections being a major indication for antimicrobial use in this cohort, hierarchical clustering identified a cluster of clarithromycin, β -lactam- β -lactamase inhibitors, amoxicillin, and doxycycline in patients receiving ward-level care (figure 3C). The strongest correlation for co-receipt was between co-amoxiclav and clarithromycin (Jaccard similarity coefficient 0.29). We observed a similar cluster in patients admitted to critical care, but this did not include amoxicillin or doxycycline (figure 3D). A cluster of the combination of a glycopeptide with ciprofloxacin was observed in patients receiving both ward-level (figure 3C)

and critical care (figure 3D). Among patients admitted to critical care, a high proportion received piperacillin-tazobactam, carbapenems, and glycopeptides, with evidence of co-prescription of carbapenem and glycopeptide (figure 3D), as well as piperacillin-tazobactam and carbapenem (figure 3D). Carbapenems accounted for 3.8% of all prescriptions, whereas carbapenem-sparing Gram-negative active alternatives¹⁴ were less frequently prescribed (co-trimoxazole 1.5%, temocillin 0.3%, and aztreonam 0.2%). Almost half of prescriptions involved WHO AWaRe watch antimicrobials (appendix p 8).

Discussion

In this multicentre, prospective cohort of 48 902 patients admitted to hospital with COVID-19, microbiologically confirmed infections were infrequent (1107 patients). Co-infection at hospital admission was rare and when infections were identified, most were secondary. Gram-negative organisms and *S aureus* were the most frequently recovered pathogens from respiratory and blood cultures. These findings have implications for empirical therapy, indicating a need to treat Gram-negative bacteria and *S aureus* empirically until culture results are available. Most patients received antimicrobials, which were commonly broad spectrum. We found geographical heterogeneity in antimicrobial usage, reflecting variations in regional and local practices.

Our findings support and add granularity to those of a living systematic review and meta-analysis of 38 studies that examined bacterial infections in patients with COVID-19.⁸ Langford and colleagues reported a pooled prevalence of confirmed bacterial infections of 8.0% (95% CI 6.1–9.9), with a higher prevalence of secondary infections (16.0%, 12.4–19.6) than co-infections (4.9%, 2.6–7.1).⁸ Although this meta-analysis included more than 6000 patients, most of the included studies were retrospective and small (13 studies had <50 patients). Moreover, the timing of infection, microbiological details, and antimicrobial use were infrequently reported. By contrast, we included microbiological data derived from standardised laboratory investigations¹⁵ from a cohort of nearly 50 000 patients. We restricted analyses to clinically significant results, correlated with the timing of sample collection, and described antimicrobial use over time and by geographical region. The multicentre design of our study improves the generalisability of our findings.

The pattern of infection and associated pathogens in our cohort of patients with COVID-19 differs from that reported in influenza. *S aureus* and *H influenzae* were the most common (but infrequent) co-infecting respiratory pathogens, and bacteria identified in secondary infections and critical care were predominantly Gram-negative organisms, including Enterobacteriaceae and *Paeruginosa*, in addition to *S aureus* (ie, organisms typically identified in hospital-acquired or ventilator-acquired pneumonia). By contrast, bacterial co-infections are much more common among patients with severe influenza,¹ and are

predominantly caused by *S pneumoniae* or *S aureus*.¹ Other studies of patients with COVID-19 have identified *S aureus* as a frequent cause of infection, including bacteraemia. We were unable to definitively determine the sources of bacteraemia in our study. However, in a case series of *S aureus* bacteraemia in 41 patients with COVID-19, most cases of bacteraemia were of unknown origin (69%), followed by pneumonia (19%), then vascular causes, including vascular access devices (7.1%).¹⁶ Exclusion of coagulase-negative staphylococci from our analysis might have led to the under-ascertainment of central line-associated bloodstream infections.

Despite little evidence of bacterial infections in our cohort, a high proportion of patients received antimicrobials. This finding is consistent with a meta-analysis that reported a pooled prevalence of antimicrobial usage of around 75% in patients with COVID-19.⁹ Elevated C-reactive protein and radiological pulmonary infiltrates are often used to differentiate bacterial from viral causes in community-acquired pneumonia. However, both of these findings are commonly present in patients with COVID-19.^{17,18} In a Scottish survey, C-reactive protein levels of at least 100 mg/L and chronic obstructive pulmonary disease or chronic lung disease were positively associated with antimicrobial prescribing.¹⁹ Combined with high morbidity and mortality, the absence of effective therapeutic options for COVID-19 during the study period, and clinical uncertainty during acute illness, high rates of antimicrobial prescription are unsurprising. Nevertheless, the infrequency of confirmed co-infection supports restrictive empirical antimicrobial usage. Antimicrobials should be restricted to individuals with atypical features of COVID-19, such as purulent sputum or lobar pneumonia, or evidence of distinct non-respiratory co-infection. Blood and sputum cultures before empirical antimicrobial treatment and incorporating trends in inflammatory markers into decision making could also support judicious antimicrobial use. The absence of an elevated white cell count at baseline and antimicrobial-associated C-reactive protein reduction can exclude co-infection in around 50% of patients with COVID-19.²⁰ Procalcitonin might be an additional decision-making adjunct, using a threshold of 0.25 ng/mL or less to identify patients with a reduced likelihood of bacterial infection.²¹ Regular review of drug charts with discontinuation of antimicrobials if co-infection is deemed unlikely, supported by negative microbiological investigations, are also key to minimise unnecessary antimicrobial exposure. When antimicrobials are required, the choice of antimicrobial should be tailored to likely pathogens and local resistance patterns, with treatment duration limited to 5 days if lower respiratory tract infection is suspected.^{6,7,22} Co-prescription of glycopeptides and ciprofloxacin was identified, which we postulate is a signature of prescribing in response to penicillin allergy labels. Many patients can be de-labelled without the need for penicillin challenges, associated with reduced broad-spectrum antimicrobial use, and this

strategy should be encouraged in patients admitted to hospital with COVID-19 in advance of a potential need for antimicrobials.²³ Furthermore, we identified frequent use of broad-spectrum empirical therapy (β -lactam- β -lactamase inhibitors) for lower respiratory tract infections, empirical escalation from piperacillin-tazobactam to carbapenems in critical care, and preferential use of carbapenems over carbapenem-sparing alternatives. These findings all represent tractable targets for antimicrobial stewardship.

In contrast to other studies,²⁴ co-infection and secondary infection were not associated with inpatient mortality among patients admitted to critical care in our study. Evaluation of the association between co-infection and outcome using observational data is complex. First, a greater proportion of deaths within the study occurred early during the hospital stay; therefore, these patients had less time to undergo microbiological investigations or to acquire a secondary infection. Conversely, any observed association could be driven by prolonged treatment in hospital because of more severe disease or slower recovery—co-infection or secondary infection might simply be a marker of this. Additionally, more thorough investigations might be done in patients who appear likely to have a favourable prognosis with adequate treatment, and such patients might be younger with fewer comorbidities.

Our study has several limitations. Retrospectively assigning clinical significance to culture results can be challenging and is further restricted in this study, as clinical findings that would contribute to diagnosis of bacterial infection were not collected at the time of microbiological sampling. The absence of clinical correlation limits interpretation of the microbiological findings—eg, isolation of *E coli* from sputum could represent true infection but alternative explanations include airway colonisation or altered (post-antimicrobial) flora, particularly in patients with chronic lung disease. We were unable to differentiate colonisation from new infection for patients with chronic lung disease, as previous microbiology results were not available.

Microbiological diagnosis of bacterial or fungal co-infection is itself challenging, especially in the context of COVID-19. Fewer diagnostic procedures might have been done during the pandemic because of clinical pressure and concerns regarding health-care worker safety (particularly from aerosol generating procedures, such as bronchoalveolar lavage), and inter-site variation in microbiological sampling is likely.²⁵ Less than 20% of our cohort had microbiological investigations recorded, which is lower than reported for community-acquired pneumonia in a recent UK-wide audit (sputum and blood cultures were done in 23.6% of patients and 58.6% of patients, respectively).²⁶ Low rates of microbiological sampling in patients with COVID-19 have been reported elsewhere.²⁷ Under-ascertainment of true bacterial infection might also be due to antimicrobial receipt before sampling, as well as low sensitivity of

culture-based diagnostics. We excluded serological investigations for fungi or atypical bacteria, and urinary antigen tests for pneumococci and *Legionella* sp, as these were inconsistently recorded and the galactomannan assay cross-reacts with β -lactams.²⁸ We also lacked the data required to address the recently proposed case definition for COVID-19-associated pulmonary aspergillosis.²⁹ Furthermore, we were unable to characterise respiratory viral or *Mycoplasma pneumoniae* co-infections, as most UK laboratories discontinued routine multiplex respiratory virus PCR testing during the study period. Therefore, we might have missed fungal or atypical bacterial co-infection identified by serum or urinary antigen tests alone, and other respiratory pathogen infections usually diagnosed by PCR.

We suspect the preferential recording of positive microbiology results based on the high culture-positivity rates; this limits our ability to determine an accurate denominator (ie, total number of microbiological investigations done); thus we have refrained from prevalence estimates. This factor might partly explain the apparently low rates of microbiological investigations we observed. The timing of initiation and duration of antimicrobial therapy, and data on antibiograms of identified organisms, were not recorded. Hence, we were unable to link infections with prescribed antimicrobials or resistance patterns—eg, the proportion of *S aureus* that are meticillin resistant. Nonetheless, this proportion is likely to be low due to low meticillin-resistant *S aureus* infection rates in the UK.³⁰

In conclusion, microbiologically confirmed bacterial or fungal infections were rare in patients admitted to hospital with COVID-19 during the first wave of the pandemic in the UK. When such infections occurred, they were mostly secondary and were caused by Gram-negative organisms and *S aureus*. The epidemiology of bacterial and fungal infections might change as immunomodulatory therapy for patients with COVID-19 progresses. Short-term systemic corticosteroid use in outpatients has been associated with a small increased risk of sepsis, and IL-6 inhibition outside clinical trials is associated with increased risk of bacterial infection.^{31,32} Prospective studies with standardised and comprehensive microbiological sampling before antimicrobial treatment are needed to characterise co-infections and secondary infections in patients with COVID-19. Tractable targets for antimicrobial stewardship interventions exist and should be prioritised.

Contributors

AH, CDR, LT, PJMO, JKB, and MGS conceived the study. CJF, TMD, CE, AH, CDR, LT, RP, LM, ABD, and EMH curated the data. CJF and TMD did the formal analysis. PJMO, JKB, and MGS acquired the funding. AH, CJF, CDR, TMD, LT, RAS, DGW, EMH, ABD, PJMO, JKB, and MGS did the investigation. HEH, MG, AH, CDR, and LM were project administrators. CJF, TMD, and EMH visualised the data. AH and MGS supervised the study. AH and CDR wrote the original draft of the manuscript. AH, CDR, LT, CJF, TMD, RAS, DGW, LS, EMH, ABD, TIDS JD, JSN-V-T, PJMO, JKB, and MGS reviewed and edited the manuscript.

EMH, MGS, and JKB validated the study data. CJF, TMD, JKB, MGS, and EMH had access to the raw data. The corresponding author had full access to all the data and final responsibility for the decision to submit for publication.

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Data sharing

Access to all data and samples collected by ISARIC4C are controlled by an Independent Data and Materials Access Committee comprising representatives of research funders, academia, clinical medicine, public health, and industry. The application process for access to the data is available on the ISARIC4C website.

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